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BRIEFING PAPER

Food and Drug Administration Proposal to Restrict the Use of Selected Antibiotics at Subtherapeutic Levels in Animal Feeds

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FOOD AND DRUG ADMINISTRATION PROPOSAL TO RESTRICT THE USE OF SELECTED ANTIBIOTICS AT SUBTHERAPEUTIC LEVELS IN ANIMAL FEEDS

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INTRODUCTION

The Food and Drug Administration announced on August 29, 1977, a proposal to prohibit the routine addition of the antibiotic penicillin to animal feeds. This briefing paper attempts to place in perspective the complex and extremely controversial issue of restricting the practice of using certain antibiotics at subtherapeutic levels in animal feeds.

This paper covers the history and use of antibiotics in animal agriculture, the public health problems that might emerge from their continued use, antibiotic policy developments, current FDA proposals, economic research on restricting antibiotic use, other pending actions, and recommendations for future action.

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SUBTHERAPEUTIC USE OF ANTIBIOTICS IN ANIMAL FEEDS

Use of antibiotics to improve growth and feed efficiency in animals originated in 1949; commercialization began in 1950. Since then, 15 antibiotics and other antibacterials, either singly or in various combinations, have been approved by FDA for use in animal feeds as well as for clinical treatment of animals.

The U.S. Tariff Commission estimated 1973 production of all antibiotics for animal feed and other nonmedical uses in the United States at 8.2 million pounds compared to 12.6 million pounds produced for medicinal use.

Antibiotics are extensively used at subtherapeutic levels in feeds for poultry, swine, beef cattle, sheep, and dairy calves. Research data clearly indicate that this practice aids in the improvement of feed efficiency, increases the rate of weight gain, and prevents and controls diseases that would otherwise increase morbidity and mortality in animals. Large-scale confinement rearing of these animals has been facilitated along with all the economies of size of such operations. Further, improved feed efficiency has reduced the feed input per unit of output and has had an impact upon the demand for feed grains and other ingredients. Increased rate of weight gain has reduced the input requirements for labor and capital items.

However, placing an economic value on the benefits from the subtherapeutic use of antibiotics is difficult since the practice grew simultaneously with and complemented improvements in management skills and animal genetics, nutrition, and disease treatment. Estimating the economic benefits of antibiotics is further complicated by the lack of comparative data on disease control, particularly after sustained use. There is a need for more knowledge about the development of resistance and whether there is a need for increased dosages to maintain disease control.

Each of the animal species responds differently to the various antibiotics. Specific responses of feeding subtherapeutic levels of antibiotics are as follows:

Cattle: Antibiotics improve feed conversion and increase rate of weight gain by (1) reducing incidence of disorders in the digestive tract; (2) reducing incidence of liver abscesses; (3) aiding in the maintenance of the animal's general health and controlling of subclinical infections; and (4) controlling the disease anaplasmosis.

Swine: Use of antibiotics in swine (1) aids in the prevention and control of baby pig diseases; (2) increases rate of weight gain; (3) improves feed efficiency; and (4) improves reproductive performance.

Poultry: Low-level feeding of antibiotics to poultry will (1) increase production in layers and turkey breeders; (2) increase rate of weight gain in turkey poults and broilers; (3) improve feed efficiency; and (4) prevent onset of diseases associated with intensive rearing.

Sheep: Antibiotics are most important for lambs in feedlots to (1) improve rate of weight gain, and (2) prevent onset of diseases associated with confinement rearing.

How antibiotics work at subtherapeutic levels is not clearly understood. Three ways have been most commonly postulated, and each has varying degrees of support. They are (1) a metabolic effect, in that the antibiotics directly affect the rate or pattern of the metabolic processes in the host animal; (2) a nutrient-sparing effect in which the antibiotics may reduce the dietary requirements for certain nutrients; and (3) a disease control effect where antibiotics suppress organisms causing clinical or subclinical manifestations of disease. Although there is extensive evidence of the nutrition and antibiotic response relationship, these effects are generally considered secondary to the disease-control effect.

PUBLIC HEALTH PROBLEM

Controversy on restricting the subtherapeutic level use of antibiotics arises from the potential public health hazard of the practice. It is important to note that no distinction was made in the regulatory process between antibiotics used for human clinical medicine and use for clinical and/or disease prevention in animals. Consequently, such antibiotics as the penicillins, tetracyclines and streptomycins were approved for use for humans and animals.

It was not observed until 1955 that bacteria could develop a resistance to antibiotics. But this observation was not in connection with animal feeding of antibiotics. The passage of time and accompanying research on antibiotic resistant organisms provided the information to develop three hypotheses on how the practice of feeding antibiotics to animals could be a health hazard to other animals and to humans.

First, it is known that certain pathogenic organisms such as salmonella, existing in the gastrointestinal tract of animals, can become resistant to the antibiotic fed to the host animal at subtherapeutic levels and over time be passed into the environment and/or food to humans. Since the organisms are antibiotic resistant, the hypothesis is that should they produce infection in humans or other animals then the same antibiotic would be an ineffective means of treatment.

The second hypothesis concerns the ability of organisms to transfer antibiotic resistance to other organisms and therefore cause widespread infection among people and animals that cannot be successfully treated with the same antibiotic. Like the first hypothesis, there is only evidence to offer partial support. Transmissibility is not being seriously questioned, but there is still a lack of evidence that these new antibiotic-resistant organisms have in any way contributed to an increase in infectious diseases of people or animals.

The third hypothesis is that trace amounts of antibiotic residue in animal tissue, milk, and eggs may lead to the emergence of resistant strains of organisms in people. But evidence is also lacking. This is considered to be the least likely means of developing drug resistant bacteria. Low-level usage of antibiotics as in correctly formulated animal feed does not contribute significantly to legal residue problems. Most of the residue problems result from therapeutic antibiotic abuse or misuse of the antibiotics in formulated feed.

Proponents and opponents of the proposal to restrict use of antibiotics in animal feeds have placed different interpretations on the potential danger of the health hazard from drug resistant bacteria. Proponents admit that the drug resistant organisms may be non-infectious or less viable than their non-resistant predecessors. But they note this should not be interpreted as meaning that by selection pressures or evolution a highly infectious and viable drug resistant organism will not appear some time in the future.

Opponents point to the lack of evidence of a health hazard and in particular refer to the incidence of salmonellosis, a disease of humans caused by salmonella bacteria that are known to be becoming antibiotic resistant as a result of the use of antibiotics in feed. Cases of salmonellosis reported to the Center for Disease Control (CDC) in Atlanta, Georgia, are indicated in the following table. As such, they are probably

Number and incidence of reported salmonellosis cases
1966-1975

Year	No. of cases	Cases per 100,000 people
1966	16,841	8.60
1967	18,120	9.16
1968	16,514	8.26
1969	18,419	9.12
1970	22,096	10.84
1971	21,928	10.63
1972	22,151	10.64
1973	23,818	11.35
1974	21,980	10.40
1975	22,612	10.61

SOURCE: Center for Disease Control, HEW

a fraction of the number of actual cases. One estimate based on these reported cases puts the total number of cases of salmonellosis in the United States at approximately 2 million a year. Many of these go unreported because the symptoms experienced are often attributed to "the flu" or an "upset stomach."

Prior to 1966, salmonellosis was not classified as a reportable disease and was grouped with other intestinal illnesses. Since 1966, however, it has been specifically reported as a separate disease. The number of cases and incidence of salmonellosis increased between 1966 and 1970 and has remained roughly constant since. The increase in the annual number of cases between 1966 and 1970 is probably due to improved reporting. As the reporting network between the State and local health departments and the CDC improved, the number of reported cases increased. Proponents also note there has been no change in antibiotic resistance demonstrated in the treatment of human cases. The same antibiotics have been effective for years.

In cases of human salmonellosis caused by raw meat or poultry products, the source of contamination is usually from the animal. Unavoidable cross- or direct contamination of raw meat or poultry can occur during slaughter. Salmonella can also be transferred from raw to cooked product via contaminated handling equipment of food handlers and is often the cause of human outbreaks.

While there is substantial evidence available to validate the benefits to society from the use of antibiotics at subtherapeutic levels in animal feeds, these benefits must be weighed against the theoretical risks of creating some highly infectious and viable drug resistant organism in the future that would be very harmful to human and animal health.

ANTIBIOTIC POLICY DEVELOPMENT

Great Britain has made an extensive study of the antibiotics situation and has adopted several changes in drug policy. In 1968, the Swann Committee was appointed to investigate the matter of subtherapeutic use of antibiotics in animal feed and make recommendations following an epidemic of Salmonella typhimurium type 29 (food poisoning) in dairy calves that subsequently spread to humans. (It was never established that use of antibiotics in animal feeds contributed to the spread of the infection from animals to humans.)

The Committee subsequently recommended that antibiotics and other antibacterials be separated into a "feed" class and a "therapeutic" class. The tetracycline, penicillin, tylosin, and sulfonamide antibiotics and the antibacterial nitrofurans should be restricted to therapeutic use only and controlled by issuance of veterinary prescription. Antibiotics such as bacitracin, flavomycin, virginiamycin, and nitrovin would be used exclusively as "feed" antibiotics subject only to recommendations pertaining to level of use.

The report was adopted by the British Government in 1971. Results of the policy change indicate that the use of drugs has been more selective and effectively monitored without sacrifice in food production. However, there is no documented evidence that there has been a reduction in disease in humans due to animal origin bacteria, that a reduction in drug resistant bacteria has improved the efficacy of therapy of human or animal diseases, or that bacterial contamination of food of animal origin has been reduced. Further, the economic effects in terms of impacts on cost of production and output are not known. Use of antibiotics and drugs in livestock and poultry feeds has not been reduced. 1/

Compared to the British, the pace of the U.S. FDA in altering the use of antimicrobial drugs has been much slower and apparently more deliberate. In 1966, the FDA completed an inquiry into veterinary medical and non-medical uses of antibiotics. The only action was the revocation of licenses to permit the direct use of antibiotics in foods for preservation purposes.

Following the Swann Committee report, FDA appointed a task force to investigate the use of antibiotics in feed. The report, published in 1972, recognized the potential health hazard of drug resistant bacteria and means of transmission to humans along with the larger problem of compromising the use of drugs for therapeutic purposes.

In 1973, FDA published a statement of policy and criteria for testing antibiotics in order to answer the questions raised by the 1972 report. 2/ Special attention was focused on the tetracyclines, streptomycin, dihydrostreptomycin, penicillin, and sulfonamides as to their effect on the salmonella reservoir in animals. Manufacturers were given until April 1975 to provide data on safety and effectiveness of products. Products that indicated a human health hazard would be withdrawn immediately.

CURRENT SITUATION

On May 27, 1977, the FDA Commissioner published in the Federal Register a notice, "Intent to Propose Rules and Call for Environmental Impact Data." FDA's general steps in the overall process to carry out this intent include:

(1) Terminate all subtherapeutic use of penicillin in all feed (proposed on Aug. 29, 1977);

(2) Terminate the use of the tetracyclines in situations where there are viable alternatives;

1/ Based on statement of Dr. R. Braude, Univ. Reading, Amer. Soc. for Animal Sci., annual meeting, 1976.

2/ Task Force Report to the FDA Commissioner on the Use of Antibiotics in Animal Feeds (FDA 72-6008) Jan. 1972.

(3) Impose restrictions on the distribution and use of the remaining uses of penicillin and tetracyclines; and

(4) Expedite implementation of the drug efficacy study implementation (DESI) notices proposing to withdraw approval of all penicillin and tetracycline combination products that lack evidence of effectiveness.

The second part of the notice was a request for environmental information from interested parties on introduction into the environment, fate in the environment, and environmental effects of penicillin and tetracyclines and other drugs that would be indirectly affected in terms of use as alternatives to penicillin and tetracyclines. The closing date for receiving information was July 26, 1977. FDA's Bureau of Veterinary Medicine indicates that it will assess the environmental data to determine if a program environmental impact statement encompassing all the actions will be required prior to finalization of the proposed actions.

On August 29, 1977, FDA proposed to prohibit the routine addition of the antibiotic penicillin to animal feeds. The proposal, appearing in the August 30 Federal Register, is the first step, according to FDA, "in a long-range FDA effort to limit the addition to animal feeds of antibiotics that are important in combating disease in people or animals." FDA allows 30 days for the public to comment and for the industry to request a hearing. There are an additional 30 allowed days to submit analysis and data to support a request for a hearing.

This proposed action, as well as others to be proposed, could have a significant impact upon the efficiency of production of cattle, swine, and poultry. According to the FDA, tetracycline, penicillin, and combinations with other antibacterials are estimated to be used in feed for all turkeys, 80 percent of the swine and veal calves, 60 percent of the cattle, and 30 percent of the chickens raised for food in the United States. However, tetracyclines are apparently used much more extensively than penicillin.

The magnitude of the impact, both in technical and economic terms will depend upon officially sanctioned types and availability of antibacterial substitutes and those specific situations where tetracyclines can be used at subtherapeutic levels where no viable alternative is known to exist. When FDA publishes an official list of substitutes and their uses and permitted uses of the tetracyclines, it will be possible to estimate the technical and economic impacts of the proposed action upon the output of animals and animal products, cost of production, and farm and retail prices.

ECONOMIC RESEARCH

Recent studies, including two by the Economic Research Service and one by FDA, report the economic consequences of restricting the use of antibiotics at subtherapeutic levels in poultry, swine, and livestock production. The Gilliam report (ERS), addressing the impact on swine and cattle production, examined the economic effects of three alternative producer reactions assuming a complete ban on the use of antibiotics at subtherapeutic levels. 3/ Although such an all-inclusive ban has never been proposed, results reveal importance of antibiotics to efficient production of livestock. For example, maintaining output at 1970 levels by either feeding the same number of animals longer or feeding more animals for the same feeding period duration would increase cattle production costs by approximately 50 cents per 100 pounds and hog production costs from $1.00 to $1.30 per 100 pounds. The impact on total annual production costs for beef and pork ranges from $370 to $470 million.

If producers increased neither the number of animals fed nor the length of the feeding period following the ban, beef and pork output would decrease and prices would increase. Consumer expenditures would increase by $1.6 billion as a result of higher prices paid for the smaller supply. Producer revenues would increase by $1.9 billion as a result of higher prices received and reductions in total costs from nonpurchase of antibiotics and feed. The study assumed 1970 prices and output levels for basis of calculation. It should be noted that, with a longer run period for adjustment, producers would probably adjust both numbers of animals and length of feeding period. As a result, the economic impact of a total ban would fall in between the ranges cited above.

Allen and Burbee addressed the impact on turkey and broiler production but used two sets of assumptions: (1) a total ban and (2) availability of antibiotic substitutes. 4/ Under the first assumption, using 1970 prices and output levels, broiler production costs would increase by 0.2 to 0.25 cents per pound while turkey production costs would increase by 0.55 to 0.9 cents per pound. Without any change in numbers of birds produced and duration of the feeding period, annual consumer expenditures would increase by approximately $200 million as a result of higher prices for the reduced meat output. Under the second assumption, statistical analyses were used to valuate the substitutability of several antibiotics. No significant difference could be found in terms of feed and growth efficacy, leading to the conclusion that a proposed restriction on use of some antibiotics would not have a significant economic impact.

Mann and Paulsen used an econometric simulation model to evaluate the impact of restricting antibiotics as animal feed additives on beef, pork, broiler, and turkey production over a 10-year period. 5/ Under the model, all the restrictive policy alternatives produced wholesale price increases. Simulation estimates of price and production cost increases, however, were lower than previous findings by the Gilliam study. This difference may be partly due to a lower estimate of the rate of feed additive use by

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3/ H. Gilliam, et. al., "Economic Consequences of Banning the Use of Antibiotics at Subtherapeutic Levels in Livestock Production," Texas A&M Univ. in cooperation with Econ. Res. Serv., Exp. Sta. Rpt. 73-2, Sept. 1973.

4/ G. Allen and C. Burbee, "Economic Consequences of the Restricted Use of Antibiotics at Subtherapeutic Levels in Broiler and Turkey Production," unpublished staff paper, Econ. Res. Serv., U.S. Dept. Agr., Nov. 1972.

5/ T. Mann and A. Paulsen, "Economic Impact of Restricting Feed Additives in Livestock and Poultry Production," Amer. J. Agr. Econ., 58(1), Feb. 1976, pp. 47-53.

producers, an assumption that would lessen the impact of a ban on feed additives. Total consumer expenditures for beef, veal, and pork were estimated to increase about $500 million over 5 years.

The use of substitute feed additives assuming equal efficacy would narrow the ranges of impact considerably. If producers elect to maintain pre-ban production levels, their adverse impact would be $74 million, with zero immediate consumer impact. On the other hand, if producers choose to maintain pre-ban feeding periods, their net gain would be $195 million and consumers would incur additional costs of $241 million.

An FDA study examined the economic consequences of restricting the subtherapeutic use of tetracyclines in feedlot cattle and swine. 6/ Impacts resulting from the use of only non-medicated feeds and from using substitute feed additives were determined. Results indicated that if producers use non-medicated feeds and maintain pre-ban production levels, the beef and pork feedlot industry would suffer an adverse impact of $680 million while consumers would experience zero, or no immediate impact. This is because the impact on producers is primarily due to increased costs which have no direct effect on the market price in the short run analyzed. In the long run, some producers may withdraw from the market or may curtail production to offset increased costs and would thus indirectly affect prices to consumers. If non-medicated feeds are used and animals are fed for the same period as before the ban, the feedlot industry in the short run would profit by $972 million and consumers would bear an adverse impact of $1,901 million.

6/ Food and Drug Administration, "Some Economic Consequences of Restricting the Subtherapeutic Use of Tetracyclines in Feedlot Cattle and Swine," OPE Study 33, Nov. 1976.

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